

# PATHOLOGY OF THE UNBORN

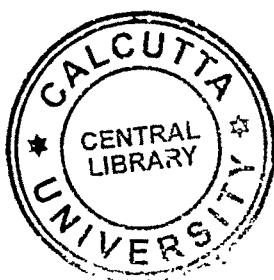
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UNIVERSITY OF CALCUTTA  
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PATHOLOGY  
OF  
THE UNBORN



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## PREFACE

This publication embodies a series of six lectures delivered in January, 1970 by Dr. Hirindrakumar Chatterjee, formerly Head of the Department of Anatomy of the Post-Graduate College of Medicine, Calcutta University, under the Khentamani-Nagendralal Endowment.

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UNIVERSITY OF CALCUTTA

### **ACKNOWLEDGEMENT**

In the preparation of this series of lectures, I gratefully acknowledge my indebtedness to a host of authors and workers on Teratology. I am particularly indebted to the following publications :—

1. "Manual of Ante-natal pathology" by J.W. Ballantyne (1904)
2. Hunterian Lectures by Sir Arthur Keith (1932)
3. "Ourselves unborn"—Terry Lectures by Prof. G.W. Cornar (1944)
4. "Mechanism of abnormal development" by P. Gruenwald. (1947)

**H. K. CHATTERJEE**

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# I

## INTRODUCTION

### *Theories and Principles of Embryogenesis*

In introducing this series of lectures on "The Pathology of the unborn," it would be worthwhile to recant in short some basic facts regarding what happens to Man from the day of his earliest advent, through the most plastic period of his development, to his birth.

Attempts would be made to present these facts in a way as to impress not only those who are interested in the science of medicine but also the scientific-minded inquisitive lay people. In doing so, I would repeat what that illustrious director of Carnegie Institute of Washington—Prof. Corner—said in prefacing his 'Terry lectures' delivered at the Yale University in 1944.

Assuming that his listeners had no previous knowledge of Biology, Prof. Corner modelled his lectures aiming at presenting a brief description of human development and its aberrations. In the hope of kindling an interest of the 'spiritualist' to this physical problem, he said, "We know from the daily gropings of our thought on human problems, that those who seek to comprehend the 'spirit' will always need to understand the 'body' first".

' Sir Thomas Browne in his 'Religio Medici' very correctly notes that "every man is some months older than hebethinks him; for we live, move and have our being in that other 'World'—the womb of our mother". It has been a recognised practice with the Chinese to give a baby at birth a full one year's credit as regards calculating its age.

Let us not forget that although kept in captivity in the womb of the mother, out of reach of human sight, the tiny little being exhibits miraculously amazing biological activities and dynamic energy.

The few months of our existence 'in utero' are the most eventful period of our life-history.

We began our life as a tiny, microscopic, unicellular 'zygote' and in 280 days, our cell-count of the body had already increased from only one at inception to two hundred billions at birth. The unicellular 'zygote'

could be found to be lost in a pin-hole but at birth the foetus attains a dimension that sometimes proves too big to be delivered normally through the birth-canal and ingenious obstetric interference has to be resorted to.

If these initial periods of our unseen existence proceed uneventfully, we, at our exit, present ourselves to the affectionate eyes of our parents as a model of developmental perfection, oblivious of the workmanship of the forces that could actually claim the credit of this faultless craftsmanship. But when this normal developmental process is disturbed, we are born as abnormal beings or 'monsters' with varying degrees of malformations ranging from the trivial to the most severe or hideous types inspiring a sense of awe and even horror.

Ballantyne (1904), in his introduction to "Ante-natal Pathology", imputes developmental deformities or monstrosities to "morbid phenomena of embryonic life" and sums up by stating that "Teratology is Embryology in disorder when vital dynamics of antenatal formative process are under the influence of some morbid agencies".

Consequently, before taking up this problem of abnormal development of the product of conception or the "Pathology of the unborn", it would be worthwhile to recant in brief the different views and hypotheses regarding some general principles of normal development.

One of the early ideas that was invoked to explain embryonic development, was the theory of "preformation", which suggested that the future organism exists in its entirety, but in an ultra-microscopic form, in the gamete itself and conception only unleashes the organism to remarkable growth. Two different theories were advanced subsequently, viz.: (1) the Homunculist and (2) the Ovulist or Ovist. In the former, it was suggested that the fully formed ultra-microscopic being lies encased in the male gamete, which after its mating with its female counterpart becomes liberated for undergoing rapid development. According to the latter theory, however, the responsibility of holding the tiny organism was attributed to the female gamete and the male one, by its union with the female, only furnished the impetus and the stimulus that were needed by the 'ovum-imprisoned organism' for further growth and development. Apparently this preformation theory rests upon the inevitable implication of an "encasement concept" very much akin to a "Chinese-box".

Driesch's (1900) finally blew up this preformation theory by his definite findings that "even separated daughter-cells" in the morula could develop into complete and perfect embryos and not fractions or parts thereof.

This observation of his was found to be possible up to sixteen-cell stage only.

Morgan (1910) advanced however a modified " preformation " theory and, while denying the existence of the actual 'physique' of the organism within the gamete, suggested that it was not the organism itself but "certain characters and traits only that were transmitted through the gametes and this again through the ' genes ' ".

The ' preformation ' theory was subsequently challenged and replaced by the theory of ' epigenesis ' which suggests that the earliest form of the organism develops from a ' formless ' beginning. This hypothesis was advanced, amongst others, by two outstanding workers—the Italian Spallanzani (1729-1799) and the German Wolff (1733-1794). It is interesting to note that the conception of ' epigenesis ' falls in a line with the earlier Hindu conception of embryonic development and echoes Aristotle's view in this regard which suggested ' formation of pattern out of apparent nothingness '.

The theory of ' epigenesis ' unequivocally declared that both male and female gametes were necessary for initiation of development of the organism and that this development takes place by progressive growth and differentiation.

But a dogmatic dependence on and advocacy of the theory of ' epigenesis ' bring us face to face with another problem—the problem of ' parthenogenesis ' which created startling interest as a result of the pioneer work of Leo Loeb (1912-15), a German Jew, who treated mature gametes of sea-urchins in hypertonic sea-water when asexual fertilisation did take place as evident from the formation of " aster-bodies " capable of undergoing cell division. Successful experiments with regard to ' parthenogenesis ' or ' fatherless ' reproduction have been carried out by Delage, Bataillon and others, and different agencies have been employed for invoking parthenogenesis, e.g., heat, hypertonic and hypotonic sea water, acidic and alkaline solutions, alkaloids, fat-solvents, radiation (ultra-violet rays, radium, mesothorium) and chemical agencies such as butyric acid, tannic acid etc. and mechanical agency in the form of a pin-prick for the purpose of replacing the essential male material to initiate developmental changes in a mature ovum akin to changes after normal fertilisation. This last led Bertrand Russell to declare parthenogenetic phenomenon as ' a pin for a father '. Be it noted however that the product of such parthenogenetic reproduction misses paternal hereditary traits and is rather attenuated in character possessing minimum requirements of material

and forces for its growth. This fact leads to a logical deduction that the paternal material appears to supply the stimulus by acting as a releaser of developmental forces very much playing the role of a finger pressing an electric switch. Thus parthenogenetic product necessarily tends to produce abnormal organism or monster.

Another factor which tends to produce abnormal development is termed 'hybridisation', where the sperm of one species successfully fertilises the ovum of another but very much akin to the former. Although the progeny resulting from 'hybridisation' does not suffer usually from the point of view of physique and physical vigour, impotency with regard to fertility has been found to result as a constant factor.

A study of some basic principles of development reveals that normal growth of the embryo does not exhibit any haphazard process of development which would usher in a state of developmental anarchy and confusion but follows some well-laid principles resulting in the formation of a normal and perfect organism.

One of these factors which perhaps is the earliest one to influence developmental process is the role played by what are known as 'developmental gradients' which mean that developmental activities do not take place simultaneously over the whole extent of the embryo but there exist a regularity, a set pattern, a well defined direction as regards the process and progress of developmental activities. This has been designated as "developmental gradient".

Embryonic development however presents more than one gradient and three distinct types of gradients have been noted, *viz.*: (1) a 'cranio-caudal gradient', which indicates that some of the developmental activities start from the cranial region of the developing embryo and thence proceed caudalwards, (2) a second, designated as "dorsi-ventral gradient", suggests that certain growth-process starts from the dorsal aspect of the developing embryo and thence proceeds ventralwards, (3) a third gradient, known as, 'medio-lateral gradient', is also discernible. It indicates that growth-process starts earlier at the median region of the embryonic area in the neighbourhood of its axis and thence proceeds lateralwards, *i.e.*, towards the marginal region of the embryo.

Of these three gradients, the cranio-caudal one is the earliest as regards incidence and is timed even before the advent of gastrulation, when the fertilised ovum presents an "animal pole" cranially and a "vegetal pole" caudally.

Thus "gradients" are the 'determinators' of early developmental activities and also determine patterns of development. Cellular protoplasmic activity in the early embryo follows these "gradients" and the future of any cell depends upon its relative position with regard to these gradients.

Child, C. M. (1924) is perhaps the pioneer worker to observe the role of developmental gradients which, when normal, ensure and determine normal growth of the embryo. Huxley and Vogt, Huxley and De Beer (1934) also made valuable contributions towards the study of developmental gradients.

With the role of developmental gradients in the background, it follows that any factor that adversely affects the normal role of 'gradients' would necessarily affect normal growth process. Thus Huxley reversed dorsi-ventral gradient by application of heat on the ventral aspect of the growing embryo resulting in the production of microcephaly while excess of heat on the dorsal aspect brought about an exaggeration in caphalic growth. Similar corroborative results were also obtained by Tazelaar and De Beer. Gilchrist succeeded in producing a second neural plate on the ventral aspect of the embryo by reversing normal dorsi-ventral gradient by application of heat which raised metabolic process so as to define this second neural plate. Gilchrist's findings were later confirmed by Castelnuovo.

These experimental findings lend confirmation to the fact that developmental gradients do play a positive role in ensuring normal growth of the embryo and any aberrations thereof result in the production of developmental abnormalities or monsters.

Although the phenomenon of reproduction did not fail to rouse quite a degree of curiosity of the laity and inquisitiveness of scientific workers on Biology, although from Aristotle onwards, workers in this field were constantly on the look-out to find the determining forces and factors that influence the development of the organism and although they realised to some degree that there do exist a method, a well set-pattern in the development of the embryo and that when this set-pattern goes wrong, due to some cause or other, the product of conception appears abnormal in varying degrees—from the extreme to the negligible—from a hideous looking monster to a simple negligible malformation, the actual determining forces and factors had all the while been eluding the attempts to unravel the mystery of their abnormal genesis.

It was in the latter part of the nineteenth century that outstanding researches of a band of pioneer workers threw interesting light on the fact

that subsequent to conception, its product almost becomes master of its own destiny so far as the build of its body and organs is concerned. The first two or three weeks of embryonic life is amazingly miraculous not only as regards pace of development and initiation of astonishing achievements with regard to the build and organogenesis in the developing embryo but in the perfection of execution and faultless craftsmanship in this regard.

But what is that wonderful phenomenon, that biological magic, that amazingly interesting process which play their role in this regard ? A band of outstanding workers in the field of Biology found that the tiny little embryo was not merely a conglomeration of cells but it was, as it were, a busy factory carrying on its activity round the clock in producing certain cytogenic stimuli which could be transmitted from one embryonic part or tissue or organ to another and thereby initiate and determine subsequent morphogenesis and organogenesis.

This phenomenon has been termed "embryonic induction". The concept of this embryonic developmental activity was first noted by the illustrious German embryologist—Hans Spemann—about the year 1900 and has subsequently been worked upon by his equally illustrious student Mangold and still later by Lewis, Adelmann, Holtfreter, Leighmann followed by Needham, Brachet, Waddington, Dalcq and Chuang.

What is revealing is the fact that the power of induction of an embryonic tissue or organ (known as 'inductor') is dependent on a chemical substance produced by it and it is this substance that acts upon another presumptive tissue in determining a new structure or organ. A microscopic embryo at its very inception can therefore be looked upon as a chemical laboratory producing different chemical substances of inconceivably high potency which in their turn may initiate subsequent induction giving rise to very much like a 'chain-reaction' in inducing organogenesis of subsequent orders. As an example, it may be pointed out that the prochordal plate dorsal to the entodermal roof of the embryonic pharynx induces the formation of the fore-brain with its optic diverticuli and the distal portion of these latter induces the formation of the lens rudiment on the surface ectoderm and the lens-element by induction develops the cornéa.

Two distinct stages have been indicated in connection with the phenomenon of "induction"—an earlier stage of "evocation", i.e., the incipient formation of or just an indication of the advent of a new structure and a later stage of "organisation" that follows "evocation." The embryonic tissue element that initiates the first phase is known as 'evocator' and that for the second phase is called 'organiser'.

The formation of the nose would give a clear picture of the two phases of induction. The cranial pole of the developing fore-brain acting on the ectoderm of the fronto-nasal process produces the localised ectodermal thickening—the olfactory placode by ‘evocation’. The subsequent changes round the placode that culminate in the formation of the nose to its perfection depend upon the later stage of “organisation” which depends upon the required degree of mesodermal growth and permeation round the olfactory placode and which is induced by the “unterlagerung” or ento-mesoderm on the roof of the embryonic pharynx. If ‘evocation’ fails, the olfactory placode itself would be absent and the question of the phase of ‘organisation’ would not arise but if the second phase is absent or is defective and therefore fails to attain the normal degree of organisation, the formation of the nose is defective and a malformation exhibiting an ‘aborted nose’ would result in a dangling ‘proboscis’—an apology of a normal nose as is found in cyclop.

It follows therefore that failure in the normal phenomenon of “induction” or “organisation” would be responsible for failure in achieving perfection of development and the degree of malformation would faithfully reflect the degree of failure of embryonic evocation or organisation.

A fact that is of great scientific interest is that embryonic induction can play its part in the morphogenesis and organogenesis in the embryo only during a stipulated period of development. This period has been termed as the ‘critical period’ (periode critique of French workers). Once this period is over, embryonic tissues and organs do not respond to induction. In other words embryonic tissues and parts remain ‘plastic’ or impressionable to induction only during this critical period. On the other hand the inductive power of an inductor-tissue retains its capacity for induction only for a stipulated period.

The work of Spemann, Mangold and others has proved that the master inductor tissue in the embryo is the dorsal lip of the gastrula. Grafted under the ventral ectoderm it induces formation of :—

- (a) a notochord with somites on either side;
- (b) early kidney tubules and even lateral mesoderm;
- (c) a central nervous system—(neural plate and tube);
- (d) even an accessory gut from subjacent entoderm.

It follows therefore that birth of a normal foetus definitely implies the role of induction to have been not only normal but to a point of perfection. On the other hand, causation of certain monstrosities can

## II

### *A Chronological Reference of Writers and Workers on Teratology.*

Having considered earlier the dynamics of normal embryonic development, the basic theories of embryogenesis and the different principles in this regard, disturbances and aberrations that affect normal development of the embryo would constitute an interesting and illuminating study—"the pathology of the unborn"—the science of 'monster formation' or 'Teratology'.

"Teras" actually means "monster" and Aristotle, as early as the 4th century B.C., defined monstrosity as being "development contrary to Nature but not contrary to Nature absolutely but contrary to the most usual course of Nature."

Keith defines Teratology or the science of monsters as the science relating to "deformed and monstrous foetuses."

Before actually taking up the different concepts of teratology, it would be worthwhile to record here in short, not only the views of scientific workers in this field but also of some non-scientific writers as well—I mean philosophers and literators.

It appears that from the very antiquities, human monstrosities did not fail to attract more than a passing notice and interest, not only of biologists alone but workers in other fields e.g. philosophy and literature appear to have taken a keen interest in the problem. Human monstrosity appears to have inspired the latter in particular. This finds evidence in the description of Polyphemus—that one eyed monster of Mount Etna as referred to by Homer in his *Odyssey*. In mythological literature of the ancient Hindus, such references to monstrosities appear galore—the ten headed Ravana, the tailed Hanuman, Shiva described as Panchanan (with five faces), Brahma as Chaturmukh (with four faces), Durga as Dashabhuja (with ten upper limbs), Ganesh as Gajana (with the head of an elephant) etc. appear to depict not only the imaginary but point to observations of some monstrosities which might have only kindled—may be in a hyperbolic manner—the fanciful imagination of early writers.

Some of the natural philosophers—Hesiod (750 B.C.) and Pliny (23-79 A.D.)—have even offered explanations re-causation of monstrosity which are on record, although their conception—particularly of Pliny—appears to-day,

with our modern concept of teratology, to be ridiculous when the author attributes the causation of human monstrosities to "Nature's creation for the purpose of astonishing people and to amuse her ownself."

It is striking however to find even in those dark days of antiquities with so very little, if at all, of scientific acumen and techniques, to find the versatile giant intellect—Aristotle—who combined in himself a philosopher, a scientist, a biologist and a savant in comparative Anatomy, formulating conceptions and ideas remarkably correct re-formation of monsters. Cicero, another ancient 'philosopher-scientist' fell in a line with Aristotle and held the same views and stated that "monsters are produced according to the same laws of Nature that regulate the normal and the ordinary."

Subsequent to Aristotle and Cicero, appears a period of lull as regards studies and concepts regarding human monstrosity as expounded by these erudite scholars which continued to glow till the early 16th century side by side with the still-prevailing concept of the 'Supernatural' influencing causation of monstrosity.

By this time Hesiod and Pliny had taken the field and recorded their observations on that type of one-eyed human monster known as Cyclop.

A number of non-scientific writers—Montaigne, Fontanelle, Lecepede and Vernois enunciated their view that abnormal and monstrous organisms develop not under condition other than the natural ones, that they are equally regular in their incidence as normal organisms although they might appear otherwise.

Gregory Reich published his work on human monstrosity entitled "Margarita Philosophica" in 1508. But some of his recorded observations almost touched the ridiculous e.g. the placing of the single median eye of the cyclop above the aborted nasal homolgue—the cyclopic proboscis.

About more than a century later Licetus (1673) brought out his work on the subject of monstrosity entitled "De monstrum causis" and although some of the lapses which characterised Reich's work were got rid of, this author too could not rise above the older amusing imaginations as evident from his placing two supplementary eyes over the occiput in Cyclop.

This very century marked however the advent of an outstanding French surgeon—Ambroise Paré (1634)—a contemporary of Licetus, whose outstanding attempt was to classify causes of monstrosity. These however ranged from the ridiculously wrong to the miraculously correct. According

to Paré, the causes were listed as :—(a) Divine will, (b) Act of mischievous spirits or their agents, (c) Superfluity or subnormality of germinal sex cells, (d) Maternal trauma, (e) Mental impression of the mother during pregnancy, (f) Abnormality of position of the foetus and (g) Abnormality of the uterus.

About the same period as Paré's, could be mentioned the names of Aldrovandi, Oliver de Serres and Réamur. All of these authors noted their observations of monstrous birth and tried to advance some explanation or other.

Sylvain Régis (1690) brought out his work—"Système de Philosophie" wherein he was emphatic in his assertion that existence of primitive monstrous germ cells was responsible for production of monsters—a genetic approach to explain monstrosity.

Régis' hypothesis was stoutly supported by a galaxy of contemporary anatomists—Duvernoy, Littré, Mery, Haller, Meckel and Winslow.

Lemery, another celebrated worker however challenged the idea expounded by Régis and more particularly Winslow's advocacy of Régis' view. Lemery would attribute formation of monsters exclusively to 'physical factors' and 'maternal trauma.'

The Lemery-Winslow duel was carried on the floor of the 'Academie des Sciences' of Paris for full twenty years, when on the death of Lemery, Winslow got an ex parte verdict in his favour although a general but strong impression was left by Lemery whose assertion was supposed to be nearer truth.

Towards the latter part of 18th century, workers in the field of teratology were led to deduce that congenital malformations or monstrosities were not initiated at the very inception of development but were the result of some sort of disturbances during 'a certain period' profoundly altering early developmental process of the embryo.

Early 19th century was marked by a noticeable onward march in the field of teratology with the advent of such outstanding workers as Speer (1819), Meckel ((1822) and Huschke ((1832).

But the towering figures in the field of teratology, that stood head and shoulders above everybody were the St. Hilaires—Etienne and Isidore—the father and the son. The former may be called the father of comparative anatomy and the latter as father of modern teratology.

In 1822, the father published his "Philosophie Anatomique" and in 1832, the son brought out his superb publication "Traité de Teratologie."

Although full 138 years have since rolled by, this work remains even to-day as the Gospel in the field of teratology. Isidore also demonstrated for the first time that it was possible to produce monsters experimentally.

Subsequent to the St. Hilaires, Daresté (1891) took the field and carried further his experimental efforts to produce monsters.

The celebrated Italian worker Taruffi (1881-1895) brought out his "Storia di Teratologia" based on his work and observations on monstrosities.

It was in the latter half of the 19th century that the science of monsters opened a new vista with the advent of 'experimental teratology.' Although first conceived by the St. Hilaires, and ably nurtured later by Daresté, Warinsky and Fol (1884) appeared as more enthusiastic and dynamic workers in the field of experimental teratology.

With the beginning of the present century, the celebrated German worker Schwalbe (1906) published his famous work "Missbildungen des Menschen und der Tierre." Both Taruffi and Schalbe have classified known human monsters.

Since its first advent about the middle of the 19th century, experimental teratology has emerged as a discipline that has brought out facts and thrown interesting light and focussed an insight into the biological explanation as regards causation of monstrosities.

The early years of this century was also marked by that outstanding worker in the field of teratology—Frederich Mall (1908) who recorded his observations on his historical collection of 434 human embryos, of which as many as 163 showed abnormalities and brought out his monumental work "Origin of Human Monsters"

Of the many outstanding luminaries in this promising field of experimental embryology are included Fére (1894), Spemann (1901-1938), Stockard (1907-1921), Mangold (1923-1933), Adelmann (1929-1936), Holtfreter (1929-1934), Leplat (1913-1947), Needham (1931-1942), Ancel (1933-1947), Wolff (1933-1948), Raynaud (1943-1950) and Chuang (1944).

This passing review of the chronology of some of the outstanding workers on the study of the science of monsters from the antiquities—beginning from Aristotle—to the workers of the present century, naturally leads to the study of the evolution of the concept of teratology and the explanations and theories advanced with regard to causation of monstrosities.

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### III

#### *Concept of Teratology from the Antiquities up to the Middle Ages.*

To the biologists of the present generation, the concept of teratology and the theories as regards causation of monstrosities have undergone astounding changes when considered against the background of hypotheses and theories prevalent in the past in this regard.

Although there does not appear to exist a clear and specific demarcation between what may be considered as the past and the present, for all practical purposes, it would be convenient to accept the advent of the 16th century as the border-line between the two periods.

Monsters did not fail to attract human curiosity right from the antiquities and human intellectual ingenuity too had never spared itself to propound theories to explain incidence of monstrous birth.

In pursuing the evolution of our knowledge with regard to causation of monstrosities, one can not fail to note the progressively scientific turn that became evident with regard to rational explanation of this problem. The entire chain of theories advanced from time to time range from the 'ridiculous' in the antiquities to the 'miraculous' in this domain of biological science to-day.

In the days of remote history with human ideas shrouded in the mist of superstition, bereft of any scientific attempt to rationally explain almost all unusual phenomena of Nature, e.g. eclipses, earthquakes, comets etc., birth of monsters too was attributed to the influence of the 'Supernatural.'

Reference to legends of the past, meticulous study of customs and beliefs of savage aborigines and primitive peoples that exist even to-day are the only materials that appear as relics of these beliefs and superstitions with regard to birth of monsters. An analysis of these beliefs and superstitions in the antiquities, although they might appear ridiculous to-day, would not fail to lead one to be convinced that these people possessed undeniably a lively imagination at least and they could not be accused in all cases of indulging in "romancing and of inventing meaningless absurdities." They did not certainly spare themselves in interpreting the import of these phenomena to the best of their the then existing capabilities with the very limited rational scientific knowledge and in the absence of any dependable techniques for solving the intriguing problems they were faced with.

The earliest concepts re-causation of monstrosities was based on suggestions indicating that formation of monsters was considered to be an act of the 'Supernatural' agencies. Some would ascribe monstrosities as the 'handicraft of Gods' while others would impute monstrous birth to the influence of evil deities—to the God of the Jews and the Christians or to the Satan of the Old Testament and the evil spirit of the New. The role of Gods in this regard was suggested to have as its objective to (1) amuse themselves, (2) to exhibit the capacity of their creative powers, (3) to express their anger and dissatisfaction with men, (4) to warn mankind, (5) to chastise individuals or even nations.

Such beliefs to interpret birth of monsters as portents of events of the future, helped "divination" in foretelling some future good, but more often, evil future.

Taking the cue from the belief that birth of monsters was a divine warning, the natural corollary was that a deity must be propitiated in order to avert the impending calamity. For this purpose, in Europe in the early and the middle ages, such monstrous products were invariably killed at birth. The Greeks of Sparta threw monstrous babies into a mountain abyss. In some cases, mothers who gave birth to such deformed children were also not spared.

With advancement of civilisation and culture and with the advent of scientific knowledge and inquisitiveness, the belief that Gods were instrumental in determining causation of monstrosities gradually waned.

It was but very natural that the belief in the teratogenic role of the gods should bring in its trail a parallel conception suggesting teratogenic role of evil and malignant spirits. Such a belief in "devilish monstrosities" was found to exist in Northern, Middle and Southern Europe, where markedly deformed babies "was to be carried to a sea-beach and burried where neither men nor cattle would go." Such were the queer fancies in the 'Dark ages' as cited by De Chaillu in his work—"the Vikings and the Viking age."

Next comes the belief in the influence of the Stars and the Moon as causative factors of monstrosities. Taruffi, for example, refers to an Alexandrian astrologer of the second century—Ptolemaens Claudius—who, it is alleged, not only indicated astral conditions that determined birth of monsters but could also mention the character of the anticipated malformation.

Bestiality were also advanced as factors determining monstrosity. It has been noted in literature that about the year 1200 A.D. when a cow

gave birth to a calf said to look like "half human," the shepherd tending the cow was charged with bestiality and held responsible for procreating the monster and he was condemned to death but Magnus Albertus, that great savant of the time convincingly attributed this monstrosity "either to" a default in the material or to celestial influence" and the shepherd's life was saved.

Hybridity was another factor that was considered responsible for causation of monstrosity. Anencephalic baby was considered by the ancient Egyptians as a monkey produced by an unnatural intercourse between a human female and a male monkey. With regard to this hypothesis of hybridisation, Aristotle held the view that successful hybridisation was only possible when (1) the tenure of gestation period of the two species was the same and (2) their size was similar on an average.

Birth of such monsters produced by human mothers actually points towards a wrong identification of a real human baby profoundly deformed that makes it liable to resemble to greater or lesser degree to a different species of animal.

The moon is another heavenly body that was supposed to influence birth of monsters. Its teratogenic power became implied in the term 'moon-calf' or the German word 'Mond-kalb' which actually meant foetal monstrosity.

That birth of monstrous baby was inflicted as 'punishment for sins committed by the parents' was also a belief rampant in some early days of civilisation and an interesting instance in support of this belief is cited in early French history about Robert II (successor to Hugues Capet) who married his own cousin Bertha. In course of time the queen gave birth to a baby with the head and neck of a goose (une tête et un col d'oie). Segur as quoted by Martin in his "Histoire de monstres" (1880) suggested that it was a punishment from God for the outrageous marriage but Sismondi suggested that the monstrosity was due to 'maternal impression'—the fright caused by a papal order of excommunication of the royal pair as a punishment for this irreligious marriage.

Henricus Asteldius who published his "Grande Encyclopedie Universelle" towards the beginning of the 17th century refers to a Danish astronomer-cum-doctor who was credited to have discovered the cause of monstrosity in "comets and as precipitates of astral elements falling from the skies."

The advent of Ambroise Paré and Licetus initiated a definite challenge to the speculative astral and planetary theory of production of monsters.

It can not be denied however that along with the superstitious beliefs in the influences of the 'Supernatural' and the astral, there did exist even in the antiquities some conceptions and theories of teratogenesis which was less speculative and hypothetical and as such have therefore survived all through centuries and even to-day stand on their own.

As early as the 5th and 4th century B.C. teratogenesis was being attributed to an alteration or disturbance in any of the two or both materials—male and female. While Empedocles pointed towards the male material alone, Aristotle (384-322 B.C.) would suggest the fault in any or both male and female material and in a poetic expression stated that "the blood of the menses is the marble, the semen is the sculptor and the foetus is the statue". Alterations or disturbances in any of these two materials—male or female or both—evidently affect the ultimate product and result in monstrosity.

Thus a genetic basis of production of monstrosity did exist from the very antiquities and the great Galen (130-200 A.D.) with his despotic imposition went a step further and suggested a modification of the 'seminal theory' by stating that the right testes was responsible for producing material for a male child and the left for a female one and when a mixture of materials from both takes place a hermaphroditic monster is the result.

The Arabian Avicenna however threw a different suggestion by stating that it is the 'placement of the semen' that determines the character of the foetus. When semen is placed on the right, a boy is born, when the placing is on the left, a girl is the result while a median placing would give rise to a hermaphrodite.

There also did exist a belief among the Hebrews that if conception takes place during active menstrual period, the product would be a monster. This belief would explain the physical deformity of Vulcan to his being begotten by Jupiter when Juno was in her period.

According to Hindu conception, the menstrual period is considered to be 'unclean' for a woman and sexual intercourse is enjoined to be shunned.

The role of "pressure" in determining teratogenesis, appears to have attracted early attention even in the antiquities as from the fact that Aristotle in his 4th book makes mention of this factor in producing teratogenesis. But what is astonishing however is that even in those days when very little of scientific knowledge was available re-early developmental anatomy, the assertion made by the great scholar that such "pressure" must act during the early period (what we designate to-day as the "plastic period") of embryonic development was recognised.

Maternal trauma had been also recognised as a teratogenic cause even in those early days. Hippocrates (496-370 B.C.) in his book "De Genitura" postulates that injury to the pregnant mother does reflect on the growth of the embryo and produce deformities in the foetus.

The role of maternal impression too as a factor producing teratogenesis had been recognised quite early from the very antiquities. The geographical distribution of the belief appears to have been prevalent over the entire human race. Interesting accounts of material impression being responsible for teratogenesis among Hebrews, Greeks, Romans, Jews and Christian fathers, Asiatics, Africans and South Americans, are on record and appear even to-day as an undeniable evidence of the existence of this belief in the past only to be handed down to subsequent period.

An analysis of the beliefs and theories *re* teratogenesis, as existed from the antiquities and in the past, would be found to present a queer amalgam of the ridiculous and the rational and lead us to the portals of a new era in the field of teratology in the middle ages with the advent of Ambroise Paré and Licetus and still later with the gradual perfection of embryological techniques and scientific studies and observations on experimental teratology.

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#### IV

### *Concept of Teratology From the Middle Ages up to the Present Time*

In case of history of human evolution and culture, scientific developments and discoveries, there cannot exist any water-tight compartmentation between different periods as regards their progress and evolution. Pursuit of the science of teratology too is no exception.

A meticulous perusal of the progress of this science would therefore show that the theories advanced for or speculated upon the production of monsters underwent remarkable changes when traced from the antiquities down to the present day. Some were categorically rejected, some modified, some new ones added and some still remain unsolved. Be that as it may, this evolutionary process is remarkably characterised by the retention of some lingering theories of the past and formulation of some new ones commensurate with knowledge gathered from careful observations, rational explanations and progress made in the field of other allied scientific disciplines.

Although as already stated, no clear cut demarcation does exist with regard to 'the past' and the 'present', the 16th century can be taken—even though arbitrarily—as 'the beginning of the present' which marks the advent of two giants in the field of teratology—Ambroise Paré (1634) and Licetus (1673).

It would be seen that even Paré could not completely extricate himself from the meshes of the ideas of 'the past' still lingering and surging round. But he nevertheless deserves credit for bringing about a shaking with regard to the then prevalent unscientific and illogically superstitious ideas of "the past."

Paré's classification of causes of monstrosity can be broadly summed up under four principal heads, *viz.* :—(a) The forces of the supernatural—a relic of the still lingering heritage of "the past", (b) the pressure theory and maternal trauma, (c) genetic and hereditary causes and (d) influence of maternal impression.

The pressure theory was not invoked originally by Paré but did exist even during the time of Hippocrates when he, in his book "De Genitura" suggested the idea that "ante-natal deformities might be due to causes acting mechanically upon the product of conception."

Paré's pressure theory of teratogenesis (1573) was later upheld by Francofurti (1628) who enumerated it along with other causative factors of malformations e.g. (1) faults in the material—male and female, (2) maternal imagination and (3) astral influence.

Licetus (1668) enumerated in great details the various ways in which pressure factors could act upon the product of conception within the womb-tightness of the membrances, narrowness of the womb, tumours in the pelvic cavity, presence of uterine mole, tight lacing or wearing of tight corset etc.

Régis (1690) stood more by a genetic factor and attributed incidence of monstrosities as being due to the role of monstrous germ cells.

Duverney (1706) however in attempting to explain the incidence of a 'double-monster' said that he could not subscribe to the theory of pressure-chance or a blind formative power but put forward the retrograde idea of falling back on the theory of the 'Supernatural' characterising this incidence as due to 'Divine intelligence' exhibiting the constructive resources of the Creator.

Lemery (1726) in explaining causation of twin-birth challenged the idea of the 'role of monstrous cells', as propounded by Régis and subsequently repeated by Duverney, but very ably invoked the pressure theory and stated that if the compressing force is a moderate one, the resulting product would show fusion of external parts and a stronger one would produce fusion of organs within the body of the two foetuses.

Winslow (1736) strongly contented Lemery's view and strongly supported Duverney. He also fought against the teratogenic role of monstrous germ cells as suggested by Régis.

The Lemery-Winslow duel which was carried on the floor of the "Academie des Sciences" in Paris and which was continued for full twenty years has already been referred to earlier. Although this tussle overshadowed the work of contemporary biologists, these latter were not sitting idle but were ranging themselves in two opposing camps. The bone of contention re Lemey-Winslow controversy too was not confined to Paris alone but moved from France to Germany, where Haller (1735), who was at first a supporter of Winslow had to admit the force in Lemery's arguments. Haller's recorded views appear in his publication "De Monstris" (1751).

Towards the end of the 18th century, the pressure theory, so ardently expounded by Lemery, appears to have received a setback particularly with Morgagni's assertion that it is foetal diseases that are directly responsible for monstrous births.

Meckel (1812) denied the role of pressure and advocated the claim of hereditary or genetic factor as the causative agency for teratogenesis.

The beginning of the 19th century saw however a revival of the mechanical or pressure theory, while quite a number of workers ranged themselves against it and supported Meckel in his views.

Maternal trauma as a teratogenic cause formed a volume of literature and numbers of cases have been reported when a pregnant mother got hurt and produced a deformed child at birth. But the site of the trauma and that of the malformation in the child could not be reconciled in a large number of cases and this threw grave doubts as regards the causative action of maternal trauma on foetal malformation. Is maternal trauma then responsible for creating maternal impressions and bringing about teratogenesis?

The advent of the 19th century was marked by a noticeable orientation as regards the study of the science of monsters. Some of the earlier hypotheses *re* the role played by the supernatural, the astral influence, mysticism and superstitions could no more be acceptable to the gradually evolving scientific minds which were on the look out for a dependable, rational and scientific etiology for causation of monsters. The inevitable first approaches for this purpose were (1) a close observation and morphological study of the anatomical features of monsters and on this basis, (2) attempt at a rational classification of monsters while pari-passu with these, (3) the inquisitive scientific minds were constantly on the look-out to find the causative factors that were considered responsible for monstrous births. Speer (1819), Meckel (1822) and Huschke (1832) were perhaps the pioneers in this century in giving this new orientation and suggest a rational approach to the study of the science of monsters.

It is to Meckel that can be attributed the credit of giving an embryological bias to the study of monsters in his book "Handbuch des Pathologischen Anatomie." He categorically repudiated all claims of the still lingering belief in 'mysticism' with regard to formation of monsters.

To the illustrious junior St. Hilaire, Isidore (1832), goes the credit of not only a meticulous morphological study and, on that basis, a classification of monsters but of the initial success that he achieved in his maiden ventures to produce monsters by human endeavours 'experimentally'—Man replacing God and Devil, stars and the moon in production of monsters.

This maiden attempt of Isidore opened up a new vista in the domain of teratology and this scientific venture was pushed ahead with grit and deter-

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mination by Daresté (1880), whose investigations led him to assert that "developmental anomalies are but the result of disturbances in the normal process of embryonic development—disturbances which affect one or more organs and *supervene at a particular period of development.*"

Thus the concept of teratology presented a definitely remarkable swing towards the rational thanks to the ushering in of revolutionary discoveries in the field of experimental teratology.

In the present century, a scintillating chain of luminaries in the field of study of embryonic development—normal and more particularly abnormal—begins with F. Mall (1908) who asserted that "no matter how fully protected the embryo might be in the uterus, it is nevertheless under the influence of teratogenic influences" but he was careful in stating also that such influences *must be acting at the 'critical' period of its development.*"

Mall's deductions regarding production of human malformations had corroborative support by a host of workers of whose work Mall was fully acquainted. They were Jacques Loeb, Wilson, Morgan and Stockard.

Mall tried to explain incidence of monstrosities basing on the background of the teratogenic factors as indicated by these teratologists—mostly experimental—and suggested that the fertilised human egg-cell has the possibility of producing an abnormal embryo if the environment and circumstances are abnormal at the 'critical period' of its development. In this regard Mall cited (a) nutritional deficiencies and (b) faulty implantation as teratogenic causes.

Although heredity was recognised as a genetic factor that plays a role in determining malformations, in the tussle between heredity and environment, Mall was almost entirely for giving preference to the latter.

With the epoch-making experiments of Hans Spemann (1901-1938) establishing the role of 'embryonic induction' ably carried on subsequently by Mangold (1923-1933), Adelmann (1929-1936), Leplat (1913-1947) and Holtfreter (1929-1934), developmental malformations began to be explained to be caused by disturbance in the normal process and role of embryonic induction and their views were firmly established in their successful attempts at production of monsters experimentally in the laboratory.

Needham (1931), Woerdeman (1929), Brachet (1947) and Chuang (1944) recorded their views on teratogenesis based on the particular role of chemical induction affecting embryogenesis.

After a meticulous analysis and careful consideration of the various theories advanced with regard to causation of monstrosities, Corner (1944)

refused to swing between God and the Devil, stars and the moon and advanced his reasons for such an attitude stating that " science has learnt in the past 400 years that the forces of good and evil in this world take effect through natural causes." He drew up a list of causes of monstrosities as :—

I. Defect in fertilisation—Irrregular fertilisation.

II. Defects in maternal environment :—

- (a) Faulty transportation.
- (b) Failure in hormone system.
- (c) Mechanical disturbance in the uterus.
- (d) Infection in the reproductive tract.
- (e) Infectious disease of the embryo.
- (f) Action of toxins.
- (g) Nutritional defects—maternal and foetal.

III. Defects in the egg, the sperm and the embryo :—

- (a) Genetic defect.
- (b) Non-genetic constitutional defect.

What Corner suggests, in his classification, as irregular fertilisation is perhaps " multi-spermial impregnation " or " poly-oval fertilisation." It is perhaps this phenomenon that was designated 400 years ago by Ambroise Paré as " excess of the seed."

'Transport-defect' as referred to by Corner evidently points to delayed arrival of the fertilised ovum at its normal destination. This may be due to mucosal defect in the uterine tube or the insufficient propulsive capacity of its musculature—some teratogenic cause such as simple constricting force or pressure playing its role in the meantime as a factor influencing the early zygote during its critical period of development.

Regarding the role of "hormone," particular emphasis relates to defective corpus luteum which plays a singular role in ensuring a suitable 'environment' and assuring a safe-implantation of the zygote. When this hormone-failure is marked it causes death of the embryo but should this failure be transitory and partial and that again taking place at the 'critical period,' the causation of developmental abnormality poses as more than a hypothetical possibility.

Mechanical factor, as a teratogenic cause affecting normal development of the embryo 'in utero,' is not exclusively a factor pertaining to modern concept of teratology, since this factor playing an etiological role

in teratogenesis dates from Hippocrates as is evident in his book "De Genitura." This factor may range from the insignificant which barely produces, if at all, any monstrous feature worthy of note to the most serious ones that culminate in producing very serious deformities. Want of adequate space for the growing embryo as pointed out by Parè centuries ago, is still considered as playing an important teratogenic role. If this pressure is of a marked degree due to extreme want of space for the growing embryo, expulsion of the organism results in the 2nd or the 3rd month but if retained, it becomes a teratogenic factor and results in the production of foetal malformations.

Infection of the uterus can certainly produce adverse effects on the early developing embryo. Although it might be possible for an organism to grow and undergo implantation unaffected by infected uterus, this causative factor might be sufficient enough to produce anomalous growth of different degrees of severity. Mall laid stress to this factor with quite a degree of emphasis.

That "eruptive fevers"—e.g. small-pox and particularly rubella or German measles play a teratogenic role particularly if the mother suffers from the disease during the first two months of pregnancy, has been well established.

This subject was first worked upon by Gragg (1941) and confirmed by Swan (1943) who found that at least 25% of pregnant mothers affected by rubella did give birth to foetus with developmental malformations. It was however noted that when such mothers suffered from the disease later than the 3rd month of pregnancy, no abnormalities were noticed. This points to the fact that there does exist a 'critical period' when the product of conception was impressionable to the teratogenic potentiality of the disease. Congenital cataract, micro-ophthalmos, micro-cephaly, congenital heart defects, deaf-mutism have been attributed to maternal rubella.

Radiation, radium and ultra-violet exposures of the mother have of late been listed as teratogenic factors. "Total monstrosities" as Mall called them were actually produced by his student Bardeen (1909) by mature sperm cells of toads x-rayed before using them to fertilise mature ova. The success in this experimentation positively points towards the teratogenic role of irradiation.

Mechanical, thermal, physical and chemical agencies as teratogenic agencies were recognised in the latter part of 19th century and their role established in this regard by the observations made in this field by almost an army of workers who would be mentioned in connection with experimental teratology.

Maternal nutritional defect and vitamin deficiencies have not only been suggested but have actually been worked upon by producing artificially dietary deficiencies and withholding necessary amount of vitamins resulting in producing developmental abnormalities. Calcium deficiency in the mothers food adversely affected the bony skeleton and teeth of the child. Caskey and Norris (1940), Landauer (1949), pointed to manganese deficiency as a cause of producing monstrosities.

The teratogenic effects of vitamin deficiency have also been fairly elaborately studied by numerous workers. Lepovsky and others (1938) found riboflavin deficiency to produce degeneration of mesonephros, oedema and anaemia in the developing chick embryo. Mason (1939) carried on experimental work on mammalian embryo affected by Vit A deficiency. Insko (1936) found fatal results produced by Vit D deficiency but these could be minimised to produce abnormalities by treating the embryo with Codliver oil. Da Zilva and others (1921) found severe defects in the hindlegs produced by withholding the fat-soluble factor which Needham (1942) attributed to Vit A deficiency. Ingier (1915), Reyher and others (1928) observed developmental abnormalities produced by Vit C deficiencies. Developmental abnormalities were also found to be produced by Vit E deficiency by Adamstone (1931) Evans et al (1927) and Urner (1930).

Gruenwald (1947) presented a classification of causes of monstrosity as follows :—

(A) Genetic causes (including influences on the germ cell) :—

- (i) Mutations—spontaneous.
- (ii) Mutation—induced by radiation, chemical agents etc.
- (iii) Hybridisation.
- (iv) Over-ripeness of the egg-cell.
- (v) Somatic mutation.

(B) Non-genetic causes :—

- (a) Mechanical agencies.
- (b) Irradiation.
- (c) Chemical agencies.
- (d) Thermal agencies.
- (e) Infections.

Gruenwald has further discussed the spatial relation of the causative agent to the part affected in producing monsters. He also suggested

three possible locations of the teratogenic agencies *viz.*—(a) within the primarily affected parts, (b) outside the primarily affected parts and (c) outside the organism.

Although the theory of heredity in relation to teratogeny, *i.e.*, the gene-theory has been recognised as playing an undoubted role in this regard and cases galore have been observed and recorded in literature of similar malformations running in a family and from generation to generation, Corner (1944) expressed the view that "it will be a very long time before enough is known about human heredity to enable a prediction of unfavourable human crosses (hybridity) except in a few obvious cases." Corner further sums up by stating "the problem of embryonic defect....in the human species is much more complicated than was formerly supposed. It is clear that in man, as in other animals, genetic and constitutional causes are operative in some cases while unfavourable maternal environment do come in the picture in causing teratogenesis."

Two particular etiological factors with regard to teratogenesis deserve special consideration—the first of these is the role of "maternal impression" in producing monsters—a hypothesis which has actually been handed down right from the antiquities through the middle ages to the present time; the second is concerned with the latest scientific venture in producing monsters in the laboratory and constitutes what is known as 'experimental embryology' which not only concerns simply production of developmental malformations but offers definitely convincing rational explanation of teratogenesis by setting at rest some of the hitherto existing speculative theories that had been haunting human mind roaming helplessly round the 'supernatural' as being responsible for teratogenesis.

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## V

### *Mother's Mind and Teratogenesis*

The mother's mind or "maternal impression" as an etiological factor in the production of monstrosities forms perhaps one of the most interesting and at the same time a most intriguing subject relating to teratogenesis. Its claim, as deserving a rightful place in this regard, as a teratogenic agency has been in existence right from the antiquities all along even up to the present time. But, as happens with theories advanced in the field of other scientific disciplines too, its claim as a recognised teratogenic agency has not been quite smooth-sailing and has been challenged, sometimes very strongly through ages. As such the causative potentiality of this agency deserves consideration as a ticklish problem that remains open still and no final verdict could be given as to its teratogenic role.

Our recent knowledge that has been accumulated, thanks to the epoch-making observations in the field of experimental teratology, appears to have successfully eliminated to some degree the empirical possibility of the mother's mind playing a role in teratogenesis but on the other hand, has provided a definite scientific basis of its teratogenic role. As such, the idle empirical acceptance as well as a rigid plea for total rejection of mother's mind playing a teratogenic role, have been given some degree of quietus to the long standing tussle that had been going on ever since the invocation of the theory of the mother's mind playing a role in teratogenesis.

The very fact that this idea has been holding its own from the antiquities and, has not only withstood persistent attempts from some quarters for its elimination from the list of teratogenic agencies but, on the other hand has successfully mobilised opinions of no ordinary workers in the field of teratology in its favour and certain revealing observations and their rational scientific explanation, all these tend to place the teratogenic role of this factor on some basis that deserves careful consideration and scientific interpretation instead of a blind, outright rejection.

That the mother's mind could have teratogenic influence on the product of conception is a belief that is almost universal in its distribution. Ploss (1892) in his book "Das Weib" refers to its cognisance as existed in China, India, East Africa, Western Asia and South America while Ballantyne

(1904) records existence of this belief among Esquimaux, Loango Negroes, old Japanese and Europeans.

In its earliest advent, this belief was not invoked to explain exactly any definite monstrosity but for interpreting minor observations e.g. change of colour and tint. Then the incidence of mother's mark and naevi being imprinted on the child was attributed as being handed down from the mother as visual conceptions influencing mother's mind. Subsequently however this theory presented a much wider application in explaining much more serious malformations and monstrosities.

Perhaps the earliest reference to maternal impression successfully influencing the developmental characteristics of the progeny dates back to ancient Hebrews as found in "Genesis XXX" which refers to the patriarch Jacob and his "tripple artifice" by which he could obtain a number of speckled cattle of a vigorous breed. By placing rods of fresh poplars, almond tree and palm tree peeled before the eyes of his flock at the time of their conception, he succeeded in getting at birth ring-shaped, speckled and spotted young ones. Although Jacob's achievement has been cited as an instance of maternal impression influencing the physique of the progeny, the influence of Providence however was not altogether discarded to explain this biological experimentation.

Fienus (1635) in his book "De Viribus Imaginationis" quotes Plutarch who refers to the Greek philosopher Empedocles (495-435 B.C.) as having stated that women who were impressed by the sight of beautiful statues during the period of conception, gave birth to equally beautiful child. Fienus makes mention of Dionysius of Syracuse who in his expectation to get an "ideal baby" got a picture of Jason hung up before the eyes of his pregnant wife. Placing of beautiful pictures and statues before the eyes of the mother at the time of conception was recommended by Lycurgus who even enunciated his 'law' enjoining Spartan carrying wives to have such pictures and statues evidently with a view to create the desired maternal impression influencing the progeny.

In supporting this "maternal impression" theory, reference has often been made of Hippocrates' assertion as appears in his "De Superfoetatione" wherein it is stated 'If a mother, during her conception, exhibits a strong desire to eat earth and charcoal and actually eats these materials, the infant born of her presents marks of the materials on its forehead.' Such a devastating statement however was almost unanimously challenged by subsequent workers who would go so far as to refuse to assign authorship of this book to Hippocrates.

Pliny (23-79 A.D.) in his work "Natural History" refers to the existence of the belief in the theory of "maternal impression" being prevalent among early Romans, Christians and Jews. This author went further and stated 'maternal impression' as a teratogenic agency operates more in the human kind than in other animals as the human "mind" is immensely superior to that of other animals as regards subtleties, receptivity of impression and faculty of imagination.

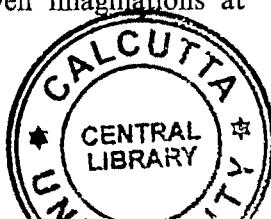
In ancient Greece, the great Galen was a definite sponsor of the idea that "maternal impression" could positively play a role in the determination of the physique of the child and recorded his view in this regard in his book—"De theriaca ad Pironem liber."

Soranus of Ephesus (98-138A.D.) also attributed birth of 'ape-like' baby to the awe-inspiring sight of a monkey at the time of conception.

Leaving aside philosophical and quasi-scientific references, glimpses of this belief would be found in the writings of Heliodorus—a romance-writer in his "AEthiopica" where the birth of Charlclea, the white daughter born of black parents—the king and queen of AEthipia—was attributed to the beautiful statue of Andromeda catching the mother's sight at the time of conception. Just the reverse of such birth—a black baby born of white parents—finds mention in "Institutiones Oratoriae" written by Quintilian.

Instances pointing towards "maternal impression" playing a role in affecting the product of conception also finds mention in the Talmud. Such view was also entertained by early christian fathers. St. Jerome stated that there is nothing astonishing in coming across a child exhibiting impressions of things actually seen or even 'imagined' by the mother at the time of conception.

Coming nearer home, in India, it would not be out of place to refer to such beliefs when we are reminded of the opinion, held out right from ancient times and persisting even to-day, which enjoins that expectant mothers in early pregnancy should shun hideous and ugly sights, awe-inspiring and horrifying spectacles, should keep the mind cheerful and gay, recall none but happy memories, think of the beautiful and the handsome and conserve a religious state of mind at the time of conception. Instances galore of monstrous birth we come across, and these in a large number of cases have been attributed to different mental states influenced by sights, past memories, thoughts and even imaginations at the time of conception or during early pregnancy.



The author cannot check the temptation of recording an instance of which he has personal knowledge and the case refers to the birth of his own cousin (son of the sister of his father). Of the mother and the father, none were of fair complexion at all. The mother was a great and voracious reader of novels and romantic literature. During her early first pregnancy she was engaged most of the day in reading the Bengali translation of Reynold's "Joseph Wilmot" in two volumes. In fact she was almost mad with the book. In course of time she gave birth to her first child, a boy who absolutely looked like a perfect European baby in complexion of his skin and hair and had blue eyes—features which were completely absent both on the maternal and paternal side of the baby. That baby is today living and is seventy six years old.

Although by the middle ages, some of the earlier concepts of teratogenesis lost their hold in being recognised as causative factors of malformation thanks to the rapid evolution of the knowledge in biological sciences, the role of 'maternal impression' however continued still to be recognised as a teratogenic factor.

The story of the French queen Bertha (wife of King Robert II) giving birth to a human monster with 'the neck and head of a goose' as referred to earlier could reasonably be attributed to the queen's extreme fright and shock produced by the order of excommunication pronounced by the Pope for the sin committed by the royal pair by cousin marriage. Damascenus imputed the birth of a 'hairy baby' as being due to its mother's mental impression produced by her intent gaze at the picture of John the Baptist wearing a hairy robe.

The Arabian physician Avicenna emphasised the fact that not only maternal impression but even that of the father could reflect on the features of the progeny by things seen at the time of conception.

The omission of this teratogenic factor in Pico's book—"Liber de imaginatione" (1505) has been imputed by Taruffi (1881) to the author's want of credulence in the theory that maternal impression can produce teratogenesis. Martin Luther however was a strong votary of the teratogenic role of maternal impression. Isidore St. Hilaire too was a believer of the teratogenic role of the mother's mind and issued caution to carrying mothers to shun looking at a monkey and anencaphalus and similar monstrosities during early pregnancy.

Lemnius in his "De miraculis oculta naturae" (1564) and Ambroise Paré in his "De monstres" (1573) strongly supported the idea of the teratogenic role of the mother's mind. Paré has also left on record illus-

trative instances in support of his contention. In one of these, the mother is reported to have given birth to a 'frog-baby' (might be a specimen of anencephaly) and Ballantyne attributed this "to the holding of a frog by the mother just before conception." Paré, like earlier workers, issued a note of caution to expectant mothers to avoid abnormal sights, shapes and figures at the time of conception or in early pregnancy.

The latter part of the 16th century abounds in votaries of this theory and mention could be made of Jean Wier (1563), Sebastian Munster (1575), Cornelius Gemma (1575), J. Rueff (1580) and others as advocates of this theory.

The 17th century could be designated as heyday for the belief that the mother's mind determined to a very large extent teratogenesis in the foetus. Credulity in this theory almost reached a maximum. It went so far as to suggest that 'conception might occur through imagination.' Quite a number of workers professed themselves as supporters of the view—Bartholin (1661), Petrus (1671) and Grass (1692) were the outstanding advocates of the theory of 'maternal impression' through imagination alone and the possibility of 'asexual reproduction.' Was it then the idea of parthenogenetic reproduction—a biological phenomenon which was yet to be explained and established on a scientific basis? The case reported by Bartholin of Magdelena, a French lady, conceiving 'in her dreams', although her husband was away from her for full four years, not only produced a stir among the scientists but the possibility and legality of the child's birth posed a problem for the Parliament of Grenoble (France) in 1637. After hearing the matron and medical men, the legitimacy of the child's birth was pronounced and the son was declared to be the legitimate heir of Augustus—his father in absentia.

Riolan (1605) was more inclined to throw his weighty opinion in favour of the teratogenic role of the mother's mind than on the still lingering belief in Divine or Satanic influence. Riolan however admitted that although the mother's mind or imagination could bring about physical teratogenesis in the progeny, it could have little effect in changing the character of the species. Fienus (1608) in his book "De Viribus Imaginationis" dealt with this theory in extenso and strongly supported it. He refers to the birth of a monstrous living child with a 'mussel-like' head as being due to his carrying mother's attraction for 'sea-mussel' as her favourite food. Other workers of this century who posed themselves as champions of the theory of maternal impression' include Schenckins (1609), Banhinus (1614), Licetus (1616), Hildanus (1646) and Seplalius (1630).

Curiously enough, it is this very same century again when a considerable volume of opinion began to be mobilised and get crystallised against this theory.

Sir Thomas Browne apparently did not even consider it worthwhile even to mention this theory as evident from complete absence of any reference to it in his book "Vulgar errors." The Italian worker Zachhia in his "Quoetiones" (as cited by Tarurffi in his 'Storia della Teratologia') positively challenged any teratogenic role of mother's mind on the basis of his argument that mother's mind being a constant factor, with some impression or other constantly haunting it, no child could be born free from some abnormality or other. Santorelli (1651) strongly contended the role of 'maternal impression' in his book—"Anteproxis Medica" and based his arguments that monsters have been born of mothers obviously completely from any 'impression.'

It is however a curious fact that almost all the 'protestants' against the "maternal impression" theory happen to belong to Italy but in those heydays of the 'impression-theory' with its triumphant onward march and unquestionable sway on the domain of teratology, the critical views and arguments of the rebel group could hardly create any material impression particularly when such illustrious workers as Aldrovandi—author of "Monstorum historia"—(1642) and Stengelius—author of "De monstris et monstrosis quam Mirabilis" (1947) not only did not discard the theory but gave it a recognised place re-malformations.

Other workers who championed the cause of "maternal impression" as playing a teratogenic role are Kerckring (1670) and Swammerdam (1672). The latter refers to a case where a lady came across a black Negro and lest this sight should have any influence on her progeny in utero was cautious enough and took a bath and scrubbed well her entire body surface except the clefts of her fingers and toes and at birth, the baby was all white except the clefts of the fingers and toes which the mother missed scrubbing.

In his book "Recherche de la Verité", Malebranche cites at least two cases—one where the birth of a baby with multiple fractures in the limb bones was imputed to its pregnant mother witnessing a criminal broken on the wheel and the other where the expectant mother in her early pregnancy was in the habit of gazing at a picture of St. Pires and in time the baby, looking very much like the saint's picture, was born.

Just a stir became discernible among teratologists towards the end of this 17th century when some of the workers were not satisfied with re-

cording cases of monstrous births and impute their causation simply to 'maternal impression' but began to think about the mechanism or the 'modus operandi' as to how does the impression act in producing monstrosity. Dolacus (1689) for instance looked for a physiological basis in this regard. In his approach to the problem, he advanced an interesting hypothesis by stating that "maternal impression was automatically conveyed to the "animal spirits" which in their turn impressed it on the early product of conception and speculated that possibly such transmission was effected through nerves. In support of his argument, he pointed to the involuntary muscular movements of the heart and the gut. The idea of Dolacus was ardently supported by Bandiera (1693).

The inception of the 18th century witnessed the tussle between the advocates and the opponents of the impression theory still going on—one group blindly in support of and the other, not only doubting but actually challenging the theory.

Duttel and Turner (1714) vigorously championed the impression theory. The former advanced some speculative anatomical explanation, while the latter, basing his observations on some cases of monstrosity, postulated certain physiological arguments—none too convincing though—in the light of our present day physiological knowledge.

The Italian Nigriosoli (1712) levelled certain arguments against the possibility of the mother's mind as playing a teratogenic role. Absence of any demonstrable direct connection between the mother and the foetus, the incidence of monstrosity in animals which are not known to possess any imagination and the birth of human monsters of mothers having no traceable 'impressions' were the arguments he fell back upon. But it was the British worker Blondel (1727) who was credited to have hurled the most effective blow to the "maternal impression" theory. He attacked his own compatriot Turner and workers in his school of thought. Blondel advanced two further arguments viz. (1) malformations do not follow even when there is positive existence of "maternal impression" during early pregnancy and (2) monstrous childbirth does occur even when 'maternal impression' could not be traceable at all.

Blondel's stand inspired a host of subsequent workers in different countries. Bellet (1745) in France, Haller (1751) in Germany, Roederer (1756) in Russia and Alexander Monro (1734)—came out as ardent supporters of Blondel's view.

But the 'maternal impression' theory still continued to hold the field particularly in some of the continental countries. Boerhave (1743) sup-

ported the theory with vehemence while Krause's (1756) dissertation on the subject presented before the Imperial Academy of Science at St. Petersburg in support of the theory brought special honour for him. Kranse's argument was based upon his assertion that there do exist nervous communication between the mother's uterus and placenta of the foetus and this influences foetal tissues which in their early stage remain remarkably plastic and therefore readily impressionable.

Von Haller (1766) challenged Krause's assertion regarding the existence of nerve communication between the uterus and the placenta. He further stated that even if such a connection were a 'vascutar' one, he categorically denied any possibility of the mother's mind or its impressions, or images and sights before the carrying mother's eyes being carried to the foetus in utero by means of a column of blood.

Morgagni (1761) was however hesitant to discard categorically the impression theory. He confessed his belief that there might exist factor responsible for the teratogenic role of 'maternal impression' which are not within our comprehension.

Thus, the closing years of the 18th century left the problematic teratogenic role of the mother's mind still open and unsettled.

The beginnings of the 19th century saw workers in the field of teratology, with regard to maternal impression playing a teratogenic role, grouped in three different camps : some holding full credence in the theory, some completely opposed to the view categorically while the third group, intelligent enough, lent qualified support to the teratogenic role of the mother's mind.

Careful research work regarding materno-foetal neuro-vascular connection revealed complete absence of any nerve or vascular connection between the mother and the foetus. As a result Kranse's school of thought was definitely eliminated.

Mesmer however took the field as a new-comer with a new hypothesis and stated that it was 'animal magnetism' which was the link between the mother and the embryo and this did not depend upon any demonstrable structural connection between the mother and the product of conception.

Inquisitive scientific minds could not afford to remain inactive or indifferent towards this intriguing problem and refused to accept or reject any of the speculative suggestions advanced from century to century which witnessed birth of monsters as a stern reality but the suggested role of the

mother's mind playing a determining role as nothing more than a speculative hypotheses.

Towards the thirtees of this century Etienne Geoffroy St. Hilaire (1827) took up an intermediate position and his equally illustrious son Isidore pushed his father's view further and asserted that "violent and sudden impressions of the mother's mind may cause monstrosity of the foetus as a result of sudden uterine contraction subjecting the fertilised ovum or the early embryo to undue pressure. When such maternal impression is moderate or feeble but is of fairly long duration, it could produce teratogenic effect on the product of conception but negligible mental reactions are not expected to have any effect in this regard. This well-reasoned hypothesis of Isidore possibly presents as a pointer in the right direction as was found by later workers, particularly of the present century, in the field of experimental teratology.

That even involuntary muscles can be profoundly influenced by strong mental impression has been known to physicians quite early. That extreme and sudden fright sometimes produces defaecation, micturition and even "premature parturition" or abortion is not unknown.

Isidore's idea provides the missing-link between the mother's mind and the product of conception by suggesting scientifically the mechanism of teratogenesis.

Vrolik (1849), a noted teratologist, was not a believer in the theory of 'maternal impression' but would impute causation of foetal monstrosity to "a severe shock producing nutritional disturbances of the mother."

Förster's (1865) argument against 'impression' theory is based on the assertion that since in most cases, monstrosities are produced utmost within a month from actual conception, the embryo has no chance of being subjected to the teratogenic influence of 'maternal impression' as the mother is ordinarily not expected to know even that conception has taken place. Another fact to which he draws attention in support of his stand is that while maternal impressions are common, monster-formation is comparatively uncommon.

The flaw in Förster's assertion is that it is not the question of the mother's knowing of her pregnancy that counts but it is simply the presence of the product of conception and the incidence of 'maternal impression' that are the cognisable factors that come into the mechanism of teratogenesis.

Martin (1880) was a strong believer in the assertion that uterine contractions produced by maternal impression brings about certain degree

of pressure on the product of conception which develops varying degrees of malformation.

While the ‘impression’ theory was to a fair extent put in a disadvantageous position in Europe, a revival of the theory was markedly noticeable by its sponsors in the states. Ballantyne mentions that no less than 170 papers were published in the states and the unquestionable majority of these upheld the impression theory.

While Müller would not believe the “impression” theory, the illustrious physiologist Burdach lent support to the view and asserted that there does exist an ‘occult relation’ between the mother and the foetus and that there does exist something like “animal magnetism” that comes into play with regard to the role of “maternal impression” in the mechanism of formation of monsters and almost echoed the view of Mesmer in this regard.

Thus the 19th century came to a close with the “maternal impression” swinging like a pendulum between the sponsors of the theory and their opponents.

Ballantyne ((1902) recorded a pessimistic note regarding the fate of the theory in the present century and preferred to maintain a non-committal attitude by judiciously stating “whether there is or there is not any truth in the theory still remains to be settled.” He also put forward two questions *viz.* :—(1) Does a definite impression upon a pregnant woman’s mind often or ever cause a defect in the foetus closely resembling the thing producing the impression ? (2) Has the state of the mother’s mind during gestation any effect upon her un-born infant’s development ? Ballantyne’s answer to his own first question is in the negative and his second in the affirmative.

One would fail to understand if there is any material difference between Ballantyne’s two questions except for the second part of his first question regarding the possibility of occurrence of a defect in the foetus closely resembling the thing producing the impression. It is evident however that Ballantyne could not totally discard the teratogenic role or disown the influence of “the mother’s state of mind during gestation.”

Some problems relating to the teratogenic potentialities of “maternal impression” appear either to have been passed over or escaped the attention of workers in the field of teratology who, with their the then limited knowledge of the ‘science of the mind’—conscious and subconscious—, could not rationally link the mind of the mother to the physique of the product of conception by suggesting the mechanism that is called into

action by the mother's mind to act upon the body of the product of conception. They have put undue emphasis and concentrated almost the whole of their energies on finding out any anatomical link between the mother and the foetus in utero and little attention appears to have been paid to mother's mind affecting the neuro-muscular mechanism that is produced by such maternal impression and its effect on the developing embryo.

The early assertion of Isidore that the involuntary musculature has a mechanical role to play in bringing about an undue pressure on the embryo offered a rational explanation and was put on an absolutely scientific basis after the startling discoveries of experimental teratologists of the present centuries. Particularly, the revealing finding of (1) Hans Spemann, who by simple application of constricting agencies round a fertilised amphibian ovum could produce varieties of monsters and (2) of Kafka (1945) who from his observations on incidence of monstrosities of early embryo in the monkey positively helped a good deal in basing the theory of 'maternal impression' on absolutely scientific basis.

According to Spemann, the degree of the constricting force, the tenure of the resulting pressure, the site of application of the constriction etc. positively determine the character of monstrosity. Kafka on the other hand asserted that such constricting force must act at a very early period of development—the plastic period of the embryo—when it is still within the uterine tube where its circular muscular fibres stimulated to contraction bring about a constricting pressure on the embryo and thus initiates teratogenesis.

It appears therefore to-day that, after the illuminating findings in experimental teratology, the theory of maternal impression refuses to be regarded as altogether speculative and as such is a hypothesis left at the mercy of fanciful thinkers in the field but holds its own thanks to our widening knowledge of physiology and the science of the mind—conscious and subconscious.

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## VI

### *Experimental Teratology*

The concept of teratology and the causes of teratogenesis when followed from the antiquities to the present day would not fail to reveal that human inquisitiveness in this regard has closely followed and has been in close consonance with the growth and evolution of other basic sciences. The first teratologists appear to have been almost helpless observers of birth of monsters and did at best record their observations advancing only the causes of occurrence of monstrosities on speculative roles bereft of any scientific basis but resting almost entirely on agencies beyond human control, such as influence of gods and devils, the moon and the stars, beliefs and superstitions etc. But such empirical hypotheses naturally could not satisfy the gradually evolving scientific and rational inquisitiveness for all times. It is an unchallenged fact that scientific minded workers refuse to remain as passive and idle spectator of things that come across their sight and they cannot but be tempted to analyse their observations against a solid scientific background and try to find out the forces or agencies that are responsible for the causation of phenomena of their observation by actual experimentation. In short they gradually became interested to find if human endeavours could bring about conditions that could produce monstrosities.

Impetus in this direction appears to have emanated from some early workers in teratology in the early 19th century. Meckel (1822) could not be reconciled to the then prevalent speculative theories regarding causation of monstrosities and in his book "Handbuch des Pathologischen Anatomie" recorded his two deductions which went a long way to inspire a school of subsequent workers. His first assertion was that malformations of the foetus represented only the persistence of earlier anatomical conditions *i.e.* they indicated failures of developmental process resulting in the foetus failing to reach its normal developmental culmination. His second deduction is of more far-reaching and novel import when he stated that "such failures in the developmental process were influenced by localised disturbance"—thereby suggesting the production of a developmental anarchy as it were.

This second deduction of Meckel ushered in an almost revolutionary idea as regards teratogenesis as, although it did not refer specifically

to what was the type and character of the 'localised disturbance' and its modus operandi, it was perhaps for the first time that the inquisitive mind of biological workers was drawn away from the stereotyped, old fangled empirical hypotheses and initiated them to give up the old beaten path of mystic surmises and conjectures and opened an altogether new vista regarding a scientific rational approach to teratogenesis.

Meckel's assertions evidently kindled a new inquisitiveness of the St. Hilaires—father Etienne and the son Indore—and set their minds in motion towards an altogether new field in the study of teratology—Experimental teratology. The idea behind this new venture in the field of study of teratology appears to be completely in tune with the gradually evolving rational and scientific inquisitiveness since it sought to produce monsters experimentally by well-controlled and well-regulated human endeavours replacing the hitherto beliefs on the speculative influence of teratogenic agencies—supernatural, mystic etc. The endeavours of biological workers came to be directed to devise definite techniques adopted in laboratories in order to produce monsters and even so far as to bring about definite patterns and types of malformations in this regard.

This task however was not so easy as it appears and full consideration of different factors had to be taken into account *viz.* :—(a) choice of the species that could be easily tackled in the laboratory, (b) choice of the sex-materials, (c) choice of the suitable technique for the preservation of sex-materials, (d) choice of incubation method, (e) choice of selection of site for subjecting it to the artificial "localised disturbance" and (f) finally the choice of the experimental technique and method to be adopted to regulate the teratogenic 'localised disturbance' at will.

The early experimental teratologist undertook his maiden attempt by experimenting on the embryos of species which are oviparous (birds) and therefore require hatching of the egg and are available at different periods of hatching.

The methods resorted to by the pioneers in this direction—the St. Hilaires, Etienne and Isidore were as follows :—

- (a) Shaking the egg mechanically in order to disturb the normalcy of the developing embryo.
- (b) Allowing the embryo to grow by changing the normal axis of the egg during hatching.
- (c) Varnishing the outer surface of the egg and thereby depriving the embryo of the requisite amount of oxygen.
- (d) Damaging the early embryo by pricking through the shell with a fine needle at various points.

And the pioneers succeeded in their maiden attempts in the new field of teratology.

Be it noted however that, as in most cases of research in any scientific subject, at the time of its inception of the venture, the initial imperfection of the techniques resorted to, the indefiniteness as regards the site of application of the method, and of its duration, etc. could not naturally be expected to specifically foretell the exact character of the monster that would result from these experimentations nor could such monsters be produced at the dictation of the researcher. But one fact was definitely settled that production of monsters was found to be no longer a monopoly of Gods and Devils, good spirits and bad ones, moons and stars, but actually did come within the orbit and the competence of human efforts.

Dareste (1855-1891), an exponent of St. Hilaires school of thought, carried ahead vigorously his ventures in the new field and apart from producing malformation by varnishing the egg during incubation period, had recourse to other methods, e.g.: (1) temporary suspension of incubation, (2) changing temperature during incubation artificially and (3) subjecting the embryo to the influence of electrical methods. An altogether new field where he initiated a maiden venture was the use of chemical agencies to bring about teratogenesis and he widely used mercurial vapour for this purpose.

Subsequent to Dareste, a host of workers actively pursued this artificial attempts at production of monsters by use of chemical agencies.

Other methods of producing monstrosities were also being resorted to. The outstanding achievements went to Warinsky and Fol (1884). They had recourse to the use of thermal agencies (thermocautery) on the early embryo. They also had recourse to mechanical agency by using a 'cutting scalpel' on the developing embryo. The monsters produced by these methods were not any new type but very much resembled the ones that were cited and described in earlier centuries. Engel (1865) used a cataract knife for inflicting minute trauma on the growing embryo and produced monsters. Lombardini (1868) used electricity for the purpose. Maggiorani (1885) invoked magnetism as a teratogenic agency and Le Blanc (1892) succeeded in getting monsters by exposing the embryo to strong light.

Thus practically all physical agencies—heat, light, electricity and even magnetism were invoked by some workers or others as teratogenic agencies in the laboratory production of monsters.

Success in attempts to produce monsters by the use of chemical agencies which was initiated by Dareste, found an energetic sponsor in Fére (1894)

who utilised quite a number of chemical substance in gaseous form—turpentine, musk, mercury, phosphorus, ammonia, ether, chloroform, alcohol, tobacco—on the egg before incubation. He also used chemical substances in solution—salt, glucose, glycerine, potassium iodide, potassium bromide, strontium bromide, peptone, creatine, xantho-creatine, cantharidin, nicotin, strychnine, sulphur, potassium cyanide and acetone which were injected in the white of the egg. Mc Clendon (1912) used different grades of alcohol for the purpose. Stockard's work (1907) in the use of chemical agencies for the production of monsters is outstandingly voluminous. He extensively used such substances as alcohol, sea water and magnesium chloride. Adelmann (1929) also used magnesium chloride and a new substance, lithium chloride, in his experiments. Werber (1915-16) used acetone and butyric acid and succeeded in producing double monsters and cyclopia. Le Plat (1919) utilised the very same material for identical purpose. Holtfreter (1933) chose sodium chloride while Leighmann (1938) and Cohen (1938) both worked with lithium salt.

The extensive use of physical and chemical agencies that were being practiced mostly in the present century or towards the close of the last one and the successful production of monsters in the laboratory established undisputed claim of these agencies as possessing teratogenic role. But the monsters they produced were non-specific in the character of their malformations nor could they be confined to any predictable area or part of the embryo. Consequently the method was designated as 'indirect' producing malformations 'at random' and not according to the will of the experimentator or according to his definite intention or anticipation.

Encouraged by the success achieved in the field of experimental teratology by the 'indirect' method as provided by chemical and physical agencies, the objective now was to produce specific types of monstrosities 'at will' where it could be possible to foretell the type of monster. This naturally needed tackling the embryo not along its whole extent but only confined to a localised area, to create 'local' disturbance and note the type of malformation produced experimentally. Such methods came to be known as 'direct' method.

Warinsky and Fol again were perhaps the earliest workers to have resorted to this 'direct' method. They performed cutting operation and removed or damaged microscopic areas of specific embryonic tissues and succeeded in producing monsters of specific type.

These laboratory manoeuvres enabled experimental embryology to earn a secure place of its own as regards production of monsters by human

efforts. Thus the close of the 19th century and the advent of the 20th presented a definite landmark in the field of teratology and workers in this field of science did not remain satisfied with the 'know-how' of their efforts but now turned their attention and focus their energies towards devising experimental techniques to produce monsters of the types planned for, locating the presumptive anlagen of different organs and structures to be tackled in producing specific malformations. Such precise and definite planning naturally needed equal definiteness as regards (1) selection of the species in specific responsive stage of development, (2) selection of the proper experimental method and technique, (3) selection of the part or region of the product of conception that is proposed to be subjected to the influence of the particular teratogenic technique, (4) determination of the duration of application of the chosen method in this regard.

Apart from locally performed micro-surgery that could ensure the objectives listed above, localised irradiation of the embryo with a micro-pencil of X-ray directed on a specific part of the embryo proved to be wonderfully efficient in the production of monsters of specific type with remarkable accuracy. Hacker and Lebedensky (1914), Bardeen, Heritwg and Baldwin (1919), Woskressensky (1928), Goldstein and Murphy (1929), Ancel and Wolff (1932), Politzer, Chambers et al (1934), Job, Leibold and Fitzmaurice (1935), Murphy and others (1942) and Raynaud (1943) not only achieved singular success in producing monsters by their irradiation technique but they—particularly the latter ones—improved their technique in this regard almost to a degree of perfection by accurately calculating the 'dose' of irradiation, locating the part irradiated and determining the definite stage of development of the embryo and foretell specifically the character of malformation that was expected to be produced.

Their observations also demonstrated that when lesser doses were used, the plastic embryonic tissue was damaged to varying degrees, the resulting organogenesis too showed correspondingly varying degrees of malformation. Application of a higher 'lethal' doses of irradiation brought about total destruction of the presumptive tissue element and consequent agenesis of the organ or structure that this part of the tissue was destined normally to develop.

Just at the beginning of this century, the celebrated German embryologist, Hans Spemann (1900) undertook his historical research work that ushered in a veritable revolution in the domain of experimental embryology and production of monster by tackling fertilised egg

in different stages of development as also different parts of the developing embryo in its most impressionable and plastic early stages. In his endeavours as regards the first series of his work, he tackled the fertilised amphibian egg. He succeeded in producing two perfect embryos by tying a knot round the fertilised ovum in the two-celled stage. When the compression of the knot was applied just in the middle of the two-celled morula—each of the two cells developed each into a complete embryo. Shifting of the site of application of the knot, he succeeded in producing different types of monstrous organism with cranial or caudal dichotomy depending upon avial application of constriction at the cranial or caudal end of the early embryo. Spemann found that graft from dorsal lip gastrula when removed and implanted on to the body of another young embryo a second independent embryo could be formed out of the graft on the host embryo. He turned this wonderful phenomenon as due to embryonic induction which plays a decisive role in normal embryogenesis and organogenesis. Spemann then logically attributed incidence of some monstrosities to failure—partial or complete of this ‘embryonic induction.’ He asserted that this phenomenon of induction can occur very much like chain-reaction in organogenesis of subsequent order. The tissue or structure responsible for induction was termed as ‘evocator’ and the structure thus ‘induced’ and which brings about organogenesis of subsequent orders became known as “organiser.”

Spemann found by his experiments that ‘induction’ to be successful in its productiveness should act at a very early stage of development when response of delicate embryonic tissue to induction is remarkable. Once this stage is passed over induction too becomes ineffective and fails to influence the phenomenon.

Spemann thus created a school of experimental embryologists or teratologists who carried their researches further and Mangold, a disciple of Spemann, did not lag very much behind her master in her experimental achievements. By undertaking micro-dissection on the roof of the embryonic pharynx cranial to the developing notochord where the entoderm of the pharyngent roof together with the mesoderm overlying the roof forms what has been termed by her as ‘unterlagernng’ or ento-mesoderm. Removal of this structure by micro-dissection was followed by the formation of a wonderful monster—a cyclop possessing a single median eye with complete or partial absence of the normal nose.

Other workers in this new field of experimental embryology and teratology are Adelmann (1934), Holtfreter (1929-34), Lewis ((1912), Giroud (1948) and they obtained revealing results.

Apart from removal of 'unterlagerung' and implanting grafts from the dorsal lip of gastropore, removal and grafting of bits of notochord to abnormal sites resulted in the formation of a segment of spinal cord in abnormal situation. Implantation of an early developing optic cup gave rise to the formation of a definite lens; graft of pronephros induced formation of mesonephros and formation of Mullerian duct resulted from a graft of Woolffian duct.

These illuminating observations that followed Spemann's pioneering achievements, now kindled a new inquisitiveness among a group of workers. They got interested in finding out the actual material contained in the graft that was specifically responsible for producing this phenomenon of induction. The endeavours in this direction were initiated by Needham (1931), Brachet (1947), Waddington, Chuang (1944) and some other workers.

Their work and research led them to assert that there does exist some superactive chemical substance in the evocator or organiser and this is responsible to initiate and produce induction.

Experimental teratology consequently opened up a new horizon with the advent of 'chemical embryology.' Research work in this field now revealed that without having recourse to micro-surgery of removal and transplantation of 'evocator' and 'organiser', induction could be produced by 'tissue extracts' obtained from these 'evocators' or 'organisers.'

We now stand to-day at the portals of a new age which promises newer and perhaps more wonderful possibilities in the field of embryology with teratology in its trail. With our ever widening scientific vision, ever increasing quest in the domain of science, ever-improving techniques, we can only await for further wonders which lie in store for us in the future.

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## VII

### *Concluding Remarks*

In introducing his series of ‘Hunterian lectures,’ (1932) on “Malformations of the human body looked at from a new point of view” Sir Arthur Keith said :

“In the earlier stages of development, ‘operations,’ which are in many respects comparable to those performed by surgeons, are carried out automatically by the tissues of the human embryo. This pre-natal Nature’s surgery may be described as knifeless, bloodless and surgeonless”. And, should I add, without any anaesthetist and operation theatre with its modern parapharnelia and equipments.

Modern research work in the field of experimental teratology is on the high roads to unravel the rationale of failure of this pre-natal surgery.

Keith states further : “Surgeons are very apt to regard this ‘pre-natal plastic surgery’ as a subject of very little direct bearing on their speciality. But just the opposite is actually the case. All the ‘pre-natal surgery’ that culminates in the development of the body of the foetus to a point of perfection, is but the result of that superbly successful surgeon—Nature—an achievement which even the most expert plastic surgeon may dream but can hardly hope to attain in practice and has got to be contented by successfully tackling lesser degrees of malformations, which could be considered, when compared with the achievement of Nature, as nothing more than ‘minor surgery.’

In conclusion, Keith notes : “It is in the hope that further extension of the methods of experimental embryology, may be applied to problems of post-natal surgery that I have made ‘Malformations of the human body,’ the subject of my lectures for the present year.”

And may I add that I chose my theme “Pathology of the unborn” as this would pinpoint our attention not only to the failures of this ‘pre-natal surgery’ that Keith speaks of, but to the very basic material—the embryo—on which this surgery is expected to be performed either marvellously and faultlessly by Nature to produce a perfect human specimen or, in case of its failure, result in the production of a ‘Monster.’

In conclusion, I may be permitted to sound an optimistic note regarding the future of the science on which I based my present series of lectures.

In the pursuit of science to-day, Man is transcending beyond his natural jurisdiction and altitude. In the remote antiquities, birth of monsters was attributed to the influence of the Supernatural. But to-day, have we not been able to "manufacture" monsters of different types in the laboratory and at our sweet will? Who knows what wonders of experimental achievements might be lying concealed in the womb of the future?

Hundred years back, when Jules Verne wrote his books—"Twenty thousand leagues under the sea" and "From the earth to the moon"—, he was mocked at and considered to be 'moon-struck'—a crack. And to-day is not the very same 'crack' the philosopher behind the actual exploration of the depths of the seas and the astounding conquest of the cosmos that has made possible landing of man on the moon?

The science of Teratology, to-day, has assumed a paramount importance not only in the field of medicine with its applied bias, but is fast developing into a promising scientific discipline standing on its own.

From the pre-historic days, almost sunk in the abyss of oblivion, and at a later period, completely swayed by superstitious beliefs and speculative concepts, the science of monsters—"Teratology"—continues its triumphant march onwards. There is a veritable thrill; a fascinating romance entwined with the origin and evolution of this science and this has made me fall in love with it.

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